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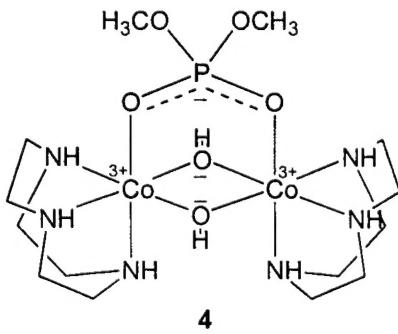
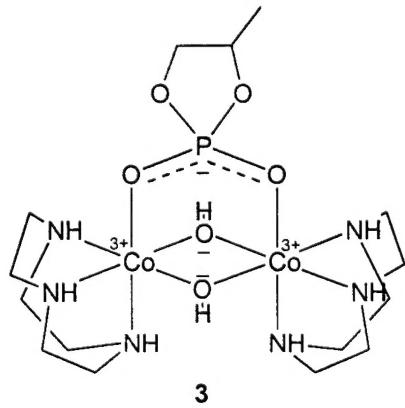
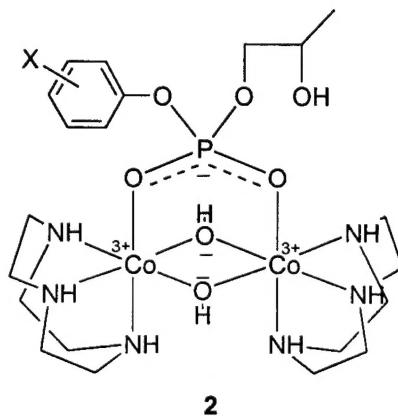
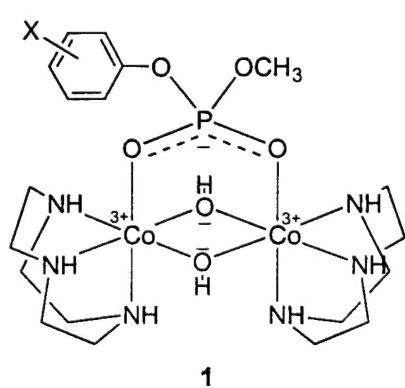
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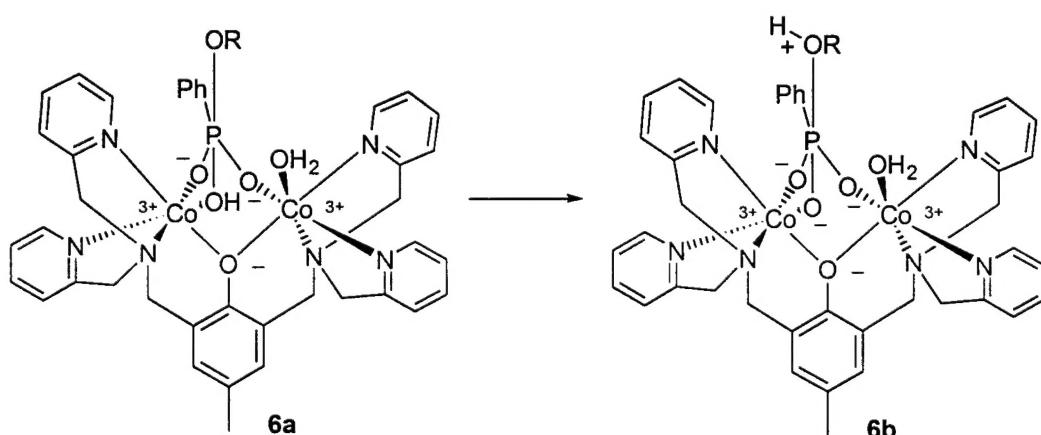
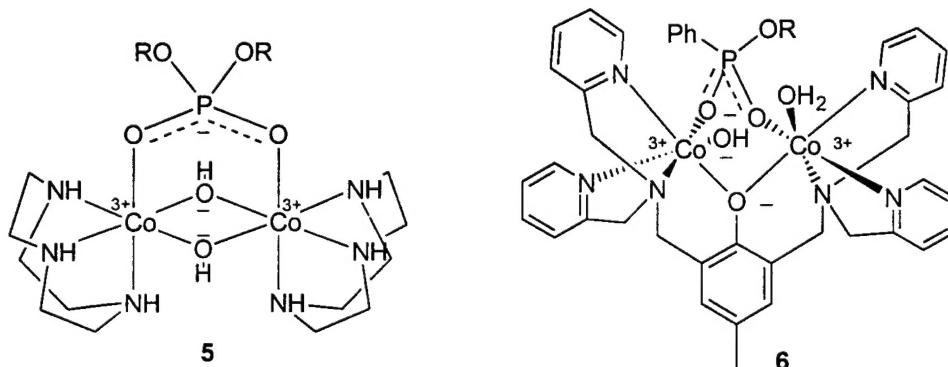
FINAL REPORT

Our first two US Army contracts (July 1, '90 to June 30, '93 & Mar 15, '94 to Mar 14 '97) involved the study of mono and dinuclear metal complexes for hydrolyzing phosphate esters. We have now completed our third US Army contract. Due to my recent move from McGill University to University of Toronto (July 1, '00), the funding period for the third contract was reduced from three to two years (July 1, '98 to June 30, '00). During this period, we continued to study the role of metal ions in phosphate hydrolysis reactions with particular emphasis on understanding *the hydrolysis of phosphates with good and poor leaving groups*. We also studied the synergistic effect between *metal coordination and H-bonding in phosphate hydrolysis*. Finally, we have been able to *dissect the role of metal ions in hydrolyzing phosphates*. Generous funding from ARO for all of the above work is greatly appreciated!

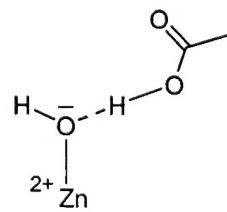
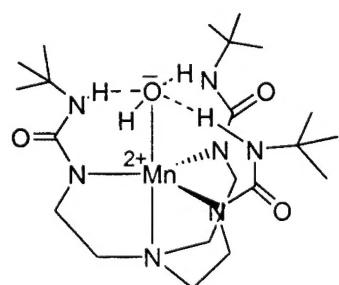
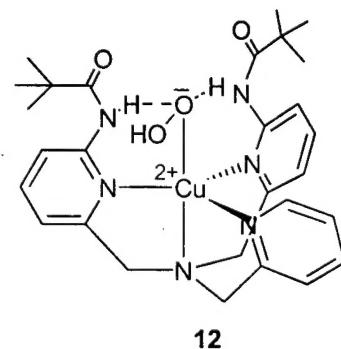
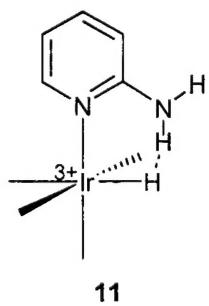
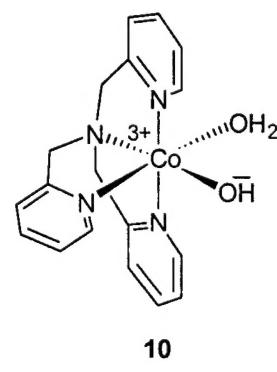
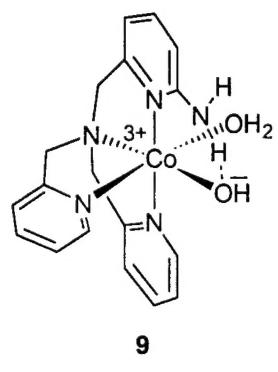
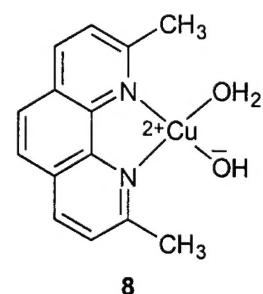
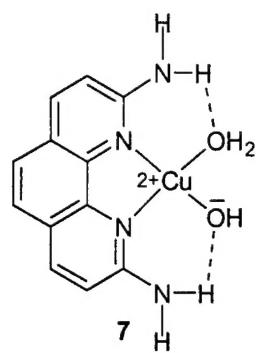
Leaving group effect. In nature there are many important phosphates with good leaving groups (ATP, soman etc) as well as those with poor leaving groups (DNA, RNA, VX etc). Thus it is of considerable interest to understand the mechanism of hydrolysis of both types of phosphates. We studied the hydrolysis of both types of phosphates bound to dinuclear cobalt complexes (**1** - **4**) and obtained valuable informations on the extent of bond making and bond breaking at the transition states.^{1,2}



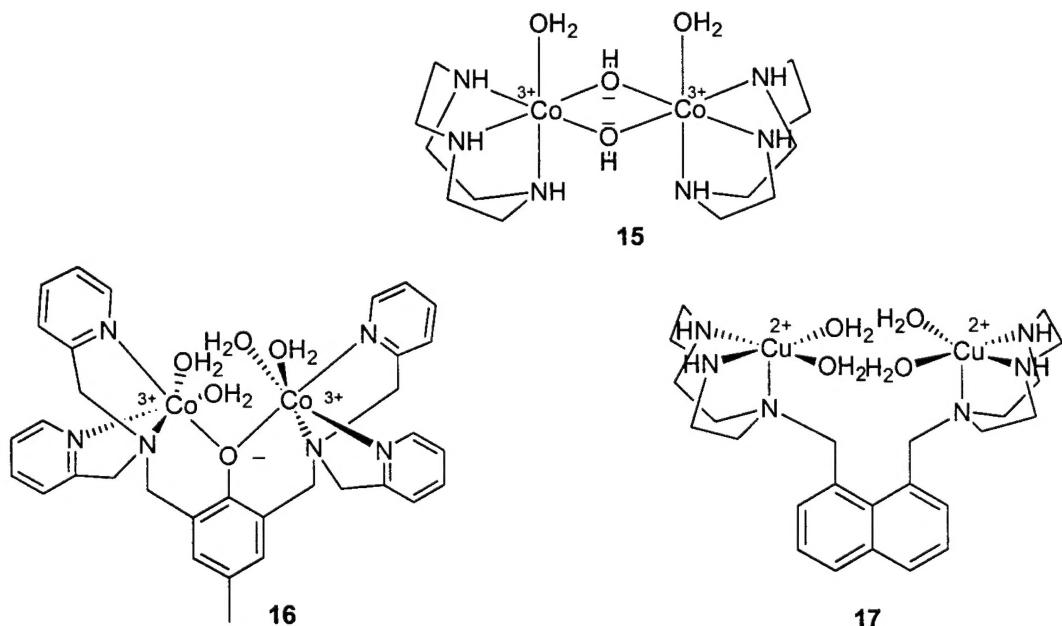
Phosphates with good leaving groups hydrolyze more rapidly in **5** than in **6**.³ In contrast, phosphates with poor leaving groups hydrolyze more rapidly in **6** than in **5**. Strongly basic leaving groups should be protonated at the transition state of the hydrolysis reaction while weakly basic leaving groups need not be protonated. In **6**, proton transfer can take place from the nucleophile to the poor leaving group (**6a** to **6b**). In **5**, proton transfer cannot take place from the nucleophile to the poor leaving group since we have shown that the nucleophile is the bridging oxide. It therefore appears that phosphates with poor leaving groups hydrolyze more rapidly in **6** than in **5** because proton transfer can take place from the nucleophile to the leaving group in **6** but not in **5**.



Hydrogen bonding. We have found that H-bonding can play an enormously important role for hydrolyzing phosphates with poor leaving groups. For example, **7** can be tens of thousands of times more reactive than **8** for hydrolyzing phosphates with poor leaving groups.⁴ Similarly we find that **9** is much more reactive than **10** for hydrolyzing phosphates with poor leaving groups. Currently there is considerable interest in metal complexes with internal H-bonds (**11 – 13**).⁵⁻⁷ Many hydrolytic metalloenzymes have been shown to contain metal-bound ligands that are hydrogen bonded (**14**).⁸ Compounds **7** and **9** represent the first model compounds that provide increased reactivity with internal H-bonding to metal coordinated ligands.



Dissecting the role of metal ions. By systematically studying the reactivity of mono and dinuclear metal complexes (15, 16, 17)⁹ it has been possible to dissect the three modes of activation that metal ions can provide for hydrolyzing phosphates. Lewis acid activation can provide about two orders of magnitude rate-acceleration while nucleophile activation and leaving group activation can provide about eight and six orders of magnitude rate-acceleration respectively.



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Report of invention: None

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Publications from previous contracts from ARO

15 Mar '94 to 14 Mar '97

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Artificial Metallo-Phosphoesterase

DAAG55-98-1-0398

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M5S 3H6

P-37670-CH

We investigated the role of metal ions in phosphate hydrolysis reactions with particular emphasis on understanding *the hydrolysis of phosphates with good and poor leaving groups*. We also studied the synergistic effect between *metal coordination and H-bonding in phosphate hydrolysis*. Finally, we have been able to *dissect the role of metal ions in hydrolyzing phosphates*.

Metal, phosphate, hydrogen bond, hydrolysis